19. An array of oligonucleotides for analysing mutations of a gene having a known nucleotide sequence, comprising a support having an impermeable surface to which are attached at different known locations a set of overlapping or partly overlapping or non-overlapping oligonucleotides which are complementary to a segment of the known nucleotide sequence of the gene.

20. The array of claim 17, 18 or 19, wherein the different known locations are spaced apart by 10-100 μm.

21. The array of claim 17, 18 or 19, wherein the oligonucleotides constitute part or all of a complete set of oligonucleotides of a predetermined length.

22. The array of claim 17, 18 or 19, wherein the entire nucleotide sequence of each oligonucleotide is predetermined.

23. The array of claim 17, 18 or 19, wherein the oligonucleotides are attached at the different known locations using a computer-controlled application device.

24. The array of claim 17, 18 or 19, wherein the oligonucleotides are attached at the different known locations using a computer-controlled application device which includes an ink-jet printer or pen plotter.

25. The array of claim 17, 18 or 19, wherein the oligonucleotides are between 8-20 nucleotides in length.

26. The array of claim 17, 18 or 19, wherein the support is made of glass.

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27. The array of claim 17, 18 or 19, wherein the support is a glass microscope slide.

28. The array of claim 17, 18 or 19, wherein, for analysing a polynucleotide of length N, the oligonucleotides of the array have a length s, wherein 4^s is an order of magnitude greater than N.

29. The array of claim 17, 18 or 19, comprising microscopic patches of microporous glass sintered on the surface of a glass plate with oligonucleotides on said microscopic patches of microporous glass.

30. The array of claim 17, 18 or 19, wherein the amount of an oligonucleotide attached on the surface of the support is dependent on its nucleotide composition.

31. The array of claim 17, 18 or 19, wherein the oligonucleotides are arranged in groups in which oligonucleotides differ by single nucleotide residues.

32. The array of claim 17, 18 or 19, wherein pairs of oligonucleotides represent allelic polymorphisms.

33. The array of claim 17, 18 or 19, wherein at least 50 pairs of oligonucleotides representing allelic polymorphisms are present.

34. The array of claim 17 or 18, for probing many different mutations simultaneously, wherein stripes of oligonucleotides are present corresponding to allelic variants to be probed.

35. The array of claim 17 or 18, for probing many different mutations simultaneously, wherein stripes of oligonucleotides are present corresponding to allelic variants to be probed such that the support carries at least one oligonucleotide stripe per mm.

36. The array of claim 19, wherein the gene is selected from the DMD gene, the HPRT gene, the Huntington's disease gene and the cystic fibrosis gene.

37. The array of claim 17, 18 or 19, wherein one part of each oligonucleotide has a predetermined sequence and another part is made up of all possible sequences.

Sub C2

38. The array of claim 17, wherein the oligonucleotides having different nucleotide sequences are attached from 72 to 10^{12} different locations on the surface of the support.

39. The array of claim 17, 18 or 19, wherein each oligonucleotide is attached by a covalent link through a terminal nucleotide residue on the surface of the support.

40. A method of making an array of oligonucleotides, which comprises:

attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support,

wherein the oligonucleotides are synthesized before attachment to the surface of the support.

41. A method of making an array of oligonucleotides, which comprises:

attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support,

wherein the oligonucleotides are synthesized in situ on the surface of the support.

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42. A method of making an array of oligonucleotides, which comprises attaching oligonucleotides to a surface of a support, the oligonucleotides having different predetermined

sequences and the oligonucleotides being attached at between 72 and 10^{12} different known locations on the surface of the support.

43. The method of claim 42, wherein the surface of the support is impermeable.

44. The method of claim 40, 41 or 42, wherein the different known locations are spaced apart by 10-100 μm.

45. The method of claim 40, 41 or 42, wherein the different oligonucleotides constitute part or all of a complete set of oligonucleotides of a predetermined length.

46. The method of claim 40, 41 or 42, wherein the entire nucleotide sequence of each oligonucleotide is predetermined.

47. The method of claim 40, 41 or 42, wherein the oligonucleotides are attached at the different known locations using a computer-controlled application device.

48. The method of claim 40, 41 or 42, wherein the oligonucleotides are attached using an ink-jet printer or pen plotter.

49. The method of claim 48, wherein the pen plotter includes a component including a polytetrafluoroethylene tube.

50. The method of claim 48, wherein the pen plotter is moved into position and the pen is lowered to lay down a coupling solution.

51. The method of claim 50, wherein the pen is filled successfully with different nucleotide precursor solutions so as to lay down oligonucleotides in groups in which oligonucleotides differ by single nucleotide residues.

52. The method of claim 40, 41 or 42, wherein the oligonucleotides are between 8-20 nucleotides in length.

53. The method of claim 40, 41 or 42, wherein the support is made of glass.

54. The method of claim 40, 41 or 42, wherein the support is a glass microscope slide.

55. The method of claim 40, 41 or 42, wherein each oligonucleotide is attached by a covalent link through a terminal nucleotide residue on the surface of the support.

56. The method of claim 40, 41 or 42, wherein the amount of an oligonucleotide attached on the surface of the support is dependent on its nucleotide composition.

57. A method of making an array of oligonucleotides, which comprises:

attaching a plurality of oligonucleotides to an impermeable surface of a support, the oligonucleotides having different predetermined sequences and being attached at different known locations on the surface of the support,

wherein stripes of oligonucleotides corresponding to allelic variants of a polynucleotide to be probed, are attached to the impermeable surface of the support, and at least one oligonucleotide stripe is attached per mm of the support.

58. A method for constructing an array of oligomers of length s and composed of n different monomers, which method comprises:

a) applying precursors for n different monomers separately to n different regions of a surface,

b) applying precursors for n different monomers separately to n different regions within each of the n different regions defined in step a), and

c) repeating the process a total of s times.

wherein a solvent repellant grid is used to divide the surface or regions thereof into different regions.

59. A method of making an array of oligonucleotides, which method comprises forming a solvent repellant grid on an impermeable surface of a support, said solvent repellant grid having exposed regions, and building the oligonucleotides on the exposed regions.

60. A method of making an oligonucleotide array, which method comprises sintering microporous glass in microscopic patches on to the surface of the glass plate, and providing oligonucleotides on said microscopic patches of microporous glass.

61. A method of making an array of oligonucleotides, which method comprises:

a) applying a mask to an impermeable surface of a support thereby to define a first exposed region of the surface to which a first nucleotide residue is coupled,

b) off-setting the mask thereby to define a second exposed region of the surface to which a second nucleotide residue is coupled, and

c) repeating step b) until the desired array of oligonucleotides has been made.

62. The method of claim 61, wherein the mask is made of silicone rubber.

63. A method of comparing polynucleotide sequences, which method comprises:

applying the polynucleotides to an array of oligonucleotides under hybridizing conditions,

wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support, and

observing the differences between the patterns of hybridisation,

wherein the polynucleotides are DNA.

64. A method of comparing polynucleotide sequences, which method comprises:

applying the polynucleotides to an array of oligonucleotides under hybridizing conditions, wherein the oligonucleotides have different predetermined sequences and are attached at different known locations on an impermeable surface of a support, and

observing the differences between the patterns of hybridisation,

wherein the polynucleotides are RNA.

65. The method of claim 63 or 64, which method additionally comprises using the observed differences to design probes for sequences that differ between the polynucleotides.

66. The method of claim 63 or 64, wherein the polynucleotides are from a normal and a mutant organism.

67. The method of claim 63 or 64, wherein the polynucleotides are from cancer cells and their normal counterparts.

68. A method of analysing a polynucleotide, which method comprises:

a) providing a first array of all possible oligonucleotides of chosen length s, such that applying a labelled polynucleotide to the array under hybridisation conditions results in about 5% labelled cells,

b) providing a second array consisting of oligonucleotides of length s+2 the sequences of which are those oligonucleotides that gave a positive signal in step a) extended by

one base in both directions, applying the polynucleotide to the second array under hybridizing conditions, and observing which oligonucleotides hybridize with the polynucleotide,

c) and optionally repeating step b) until no repeated sequences are identified.

69. The method of claim 68, wherein the oligonucleotides of the second array are those oligonucleotides identified as repeats in step a), extended by one base in both directions.

70. The method of claim 63, 64 or 68, wherein the analysis is performed by a computer programmed to compensate for variations in nucleotide composition.

71. The method of claim 63, 64 or 68, wherein the polynucleotide is amplified by the polymerase chain reaction.

72. The method of claim 71, wherein the polynucleotide is amplified from genomic DNA.

73. The method of claim 63 or 68, wherein the polynucleotide is genomic DNA.

74. The method of claim 65 or 68, wherein the polynucleotide is messenger RNA population.

75. The method of claim 63, 64 or 68, wherein the polynucleotide is tagged with a fluorescent label.

76. The method of claim 63, 64 or 68, wherein the polynucleotide is radio-labelled and hybridisations on the array are detected by autoradiography.

77. The method of claim 63, 64 or 68, wherein hybridisations are detected by means of a digitizing scanner.

78. The method of claim 63, 64 or 68, wherein hybridizations are detected by means of a device having a resolution of between 1 μm and 125 μm.

79. The method of claim 63, 64 or 68, wherein the oligonucleotides of the array constitute all or part of a complete set of oligonucleotides of predetermined length.

80. The method of claim 47, 48 or 52, which comprises using an array of oligonucleotides segregated such that the different regions have different base compositions to compensate for the differences in stability of duplexes of differing base composition.

81. The method of claim 80, in which the array is further segregated during hybridisation so that each area is exposed to different hybridisation conditions.

82. The method of claim 63, 64 or 68, wherein the polynucleotide is applied to the array under hybridisation conditions in the presence of a quaternary or tertiary amine.

83. The method of claim 82, wherein the amine is tetraethylammonium chloride used at a concentration in a range of 2M to 5.5M.

84. The method of claim 63, 64 or 68, wherein for analysing a polynucleotide of length N, there is used an array of oligonucleotides of length s, where 4^s is an order of magnitude greater than N.

85. The method of claim 63, 64 or 68, wherein the hybridisation temperature is chosen to be close to the Tm of duplexes and is controlled to better than ±0.5°C.

86. The method of claim 63, 64 or 68, wherein the oligonucleotides of the array are present in excess over the polynucleotide, so as to distinguish between hybridisations involving single and multiple occurrences of a polynucleotide sequence.

87. The method of claim 68, wherein the polynucleotide is DNA or RNA.

88. A method of reconstructing a polynucleotide sequence, by the use of an array of oligonucleotides immobilised on a surface of a support, which method comprises applying the polynucleotide to the array of oligonucleotides under hybridisation conditions:

a) finding a first oligonucleotide of the array of length s which gives a positive hybridisation signal,

b) examining the array for hybridisation to a second oligonucleotide the sequence of which overlaps the first oligonucleotide by s-1 bases,

c) optionally examining the array for hybridisation to a third oligonucleotide which overlaps the first oligonucleotide by a sequence of s-1 bases,

d) optionally continuing these steps so as to extend sequence information by one base in each direction at each step.

89. A method of analysing for a gene of known sequence, which method comprises providing an array of oligonucleotides comprising a support having an impermeable surface to which are attached at spaced locations a set of overlapping or partly overlapping or non-overlapping oligonucleotides complementary to the known sequence of the gene, applying the gene to the array under hybridisation conditions, and observing a pattern of hybridisation.

90. The method of claim 89, wherein the gene is selected from the DMD gene, the HRPT gene, the Huntington's disease gene and the cystic fibrosis gene.

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91. A method for determining the sequence of a polynucleotide, which comprises:

applying the polynucleotide to a substrate having an impermeable surface to which are immobilised a plurality of oligonucleotide probes having different predetermined sequences under hybridisation conditions, wherein the probes are immobilised at different known locations on the surface of the support such that the oligonucleotide at one known location is different from the oligonucleotide at another known location,

detecting the oligonucleotide probes to which the polynucleotide hybridizes, and

determining the sequence of the polynucleotide based upon the known sequence of the oligonucleotide probe to which the polynucleotide hybridizes.

92. The method of claim 91, wherein the polynucleotide is labelled.

93. The method of claim 91, wherein a plurality of polynucleotides are applied to the substrate.

94. The method of claim 93, wherein the plurality of polynucleotides are fragments of a gene.

95. A method for analysing multiple sequence variants in multiple polynucleotides, which comprises:

a) laying down stripes of oligonucleotides corresponding to each sequence variant on the surface of a solid support,

b) applying the polynucleotides to the surface under hybridisation conditions in stripes orthogonal to those of the oligonucleotides,

c) observing hybridisation at a site of intersection as an indication of the presence of a variant sequence in the polynucleotide.

wherein the stripes of oligonucleotides have a width of 1 mm or less and the polynucleotides are applied in orthogonal stripes about 5 mm wide.

96. A kit for analysing a polynucleotide comprising: an array of oligonucleotides comprising a support having an impermeable surface to which a plurality of oligonucleotides are attached, the oligonucleotides having different nucleotide sequences and being attached at different known locations on the surface of the support; apparatus for hybridisation of the polynucleotide to the array; and a scanner for detecting hybridisation.

97. A kit for analysing a polynucleotide comprising: an array of oligonucleotides comprising a support having a surface to which the oligonucleotides are attached, wherein oligonucleotides having different nucleotide sequences are attached at between 72 and 10^{12} different known locations on the surface of the support; apparatus for hybridisation of the polynucleotide to the array; and a scanner for detecting hybridisation.

98. A kit for analysing mutations of a gene comprising: an array of oligonucleotides having a known nucleotide sequence comprising a support having an impermeable surface to which are attached at different known locations a set of overlapping or partly overlapping or non-overlapping oligonucleotides which are complementary to a segment of the known nucleotide sequence of the gene; apparatus for hybridisation of the polynucleotide to the array; and a scanner for detecting hybridisation.

99. The kit of claim 96, 97 or 98, including also computer software and/or computer hardware for analysing the results. --

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IN THE SPECIFICATION

Cancel without prejudice pages 1-30 of the specification as filed and substitute therefor the attached substitute specification containing pages 1-21.

Furthermore, please amend the substitute specification as filed.

Page 1, line 2, delete in its entirety and insert: